

to maximize substitution at the C6 position of starch (the molar ratio of C2-C6 is 0.5-2.0, (see page 1, paragraph 3; page 2, paragraph 2). Further, a definite molar ratio of alkali starch must be used in GB 1 395 777 (at least 2.0 moles alkali to each mole of starch, see page 2, paragraph 2; page 4, paragraphs 1 and 2 and Claim 3). By contrast, the object of the process in Claims 4-7 is to substitute predominantly at C2 (see page 6, paragraph 2; page 7, paragraph 2). The pH value in the synthetic process is very important. Hydroxy ethylation is carried out in alkaline conditions at about pH 12 (Claims 4 and 5; page 8, paragraph 3; page 9, paragraph 6). Thus, it appears the compounds of Group I could not be made by the GB'377 process.

Similarly, the Examiner has provided no reason to believe the process of the Group II claims could make different products than those of Claims 1-3. That is to say, the Examiner has provided no grounds for doubting Applicants' disclosure (at page 7, paragraph 3 - page 8) that the process would result in the claimed products.

It is therefore submitted that the claims of Groups I and II are not distinct. The possibility of different classification of the groups of claims does not require this conclusion. Therefore, the Examiner is urged to withdraw the restriction requirement.

Claims 1-3 are rejected as obvious over Reference A (US Patent 4,629,698 Nitsch et al.) or Reference L (British Patent 935 339, Staley).

The plasma expander prepared according to the '698 patent (Nitsch, et al.) has a molecular weight of 40,000 to 1,000,000 and a molar substitution (MS) of from 0.1 to 0.8. The '698 patent (Nitsch, et al.) contains neither disclosure of the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units, nor any disclosure of the substitution degree (DS). Furthermore, from the statements of the '698 patent, a person having ordinary skill cannot gather whether the ratio C2/C6 is high or not and further, it is impossible to a person having ordinary skill to easily adjust this ratio.

Nevertheless, the Examiner concludes that the claimed plasma expanders would be obvious, reasoning that the compositions in Applicants' claims as well as those disclosed in Nitsch, et al., are both used as plasma expanders. From this shared usage, the Examiner deduces that the C2-C6 substitution ratio recited in Claim 1 "would have been manipulable to the practitioner... to provide maximum benefits".

The obvious gap in this reasoning is that Nitsch, et al. contain no motivation for modifying the C2/C6 ratio as claimed. Even if such a modification were present, there would still be no teaching of the substitution degree (DS) of "from 0.15 to 0.5".

Further differences in the plasma expanders are seen from the methods by which they are produced. According to US 4, 629, 698 patent (Nitsch, et al.), a starch-based plasma expanders (e.g. HES) is prepared by a combination of hydrolytic decomposition of an amylopectin-rich starch to a definite molecular weight and partial etherification to a definite molar substitution, whereby said etherification is accomplished either before or after said hydrolysis, said hydrolytic decomposition comprises hydrolysis with alpha-amylase, beta-amylase or pullulanase to a molecular weight of 40,000 to 1,000,000 Dalton

and said etherification is carried out to a molar substitution of from 0.1 to 0.8. The process of the '698 patent (Nitsch, et al.) can also be carried out in such a way that, after said hydrolytic decomposition and a subsequent etherification, a second enzymatic decomposition step can take place (see Claim 12 and Column 2, paragraph 1-3). The etherification is carried out within 2 hours (See Example 1).

In contrast to Nitsch, et al., the claimed compounds are prepared in such a way that:

- a) starch having a content of amylopectin of >95% is pre-extracted with methanol,
- b) the starch obtained is brought by acid hydrolysis to a suitable mean molecular weight,
- c) then the starch obtained is subjected to an alkali wash,
- d) the obtained starch is hydroxyethylated by means of a hydroxyethylation agent under alkaline conditions, whereby as hydroxyethylation agent 2-chloroethanol or ethylene oxide, preferably 2-chloroethanol is used and the hydroxyethylation is carried out under alkaline conditions at room temperature, wherein the pH-value is kept at a value of about 12 during the hydroxyethylation,
- e) then the molar weight of the hydroxyethylated starch is exactly set by acid hydrolysis,
- f) the hydroxyethyl starch thus obtained is purified, and
- g) spray dried.

The inventive etherification takes place within 6 to 10 hours, preferably 7 to 8 hours and during the inventive etherification, the pH-value is kept at a value of about 12 (see page 8, paragraph 3; page 9, paragraph 6). Thus, it is clear the disclosure of Nitsch, et al. produces a substantially different plasma expander.

From the statements of Nitsch, et al., it cannot be gathered which pH value will result from the disclosed conditions. Please note that the starch material to be used in the etherification according to Nitsch, et al. is pretreated in a way different from the starch material of the inventive process. However, the amount of NaOH used according to Example 1 of Nitsch, et al. would produce a pH value of higher than 13 according to the inventive process and thus would, according to the inventive process, not result in the desired ratio of C2/C6.

Moreover, the superiority of the plasma expanders of Applicants' claims to those of Nitsch, et al. is seen in comparing Figure 1 of Nitsch, et al. to page 7, paragraphs 1 and 2 of Applicants' specification. The plasma expanders recited in Claims 1-3 are clearly eliminated from the human body within 4 hours, while those of Nitsch, et al. require up

to 9 days for elimination. Applicants' claimed plasma expanders are thus unexpectedly superior to those of the reference.

The superiority of the claimed plasma expanders is demonstrated in the appended Declaration under Rule 1.132, where a plasma expander of molecular weight 500-5,000 MS 0.30; DS 0.28 and C2/C6 ratio value of 8.5 was infused into four (4) male volunteers (ages 20-40 years). Concentration of the plasma expander in the serum was determined at different times. The results indicated in the drawing show complete elimination of the claimed plasma expander within about 8 hours, that is in approximately 1/27<sup>th</sup> of the time required to eliminate the Nitsch, et al. plasma expanders.

The unexpected superiority of the claimed plasma expanders is part of the subject matter as whole of the claimed invention. Because there is no disclosure of the superiority anywhere in Nitsch, et al., an important aspect of the claimed invention is not present in the cited art. Therefore reconsideration and withdrawal of this rejection based on Nitsch, et al. are requested.

Turning to the 2nd rejection, Staley relates to the production of certain hydroxyalkyl amyloses based on reacting amylose fractionated from starch with vic-epoxy compound. Since starch may be fractionated into amylose and amylopectin, it is seen Staley employs a different starting material than Applicants' process (amylose vs. amylopectin-rich starch). Thus, Applicants' process will result in a final product different from that of Staley: hydroxyethylstarch vs. hydroxyalkylamylose.

Staley does not teach that etherification of amylopectin produces a good extender. Even if it did, Staley is silent as to the molecular weight, the substitution degree DS and the ratio of C2/C6 of the hydroxyalkylamylose. From Staley, the molecular weight substitution degree DS and the ratio C2/C6 of the hydroxyalkylamylose cannot be gathered. Thus, Staley is unable to render obvious the compounds of Applicants' Claim 1.

Staley is further distinguishable in that process has the following steps:

- a) reacting a suspension of amylose with at least 0.2 mole of a vic-epoxy compound and at least 0.04 mole of an alkaline catalyst per mole of amylose at a temperature of from 30 to 90°C, wherein the suspending liquid is a polar solvent for the vic-epoxy compound,
  - b) neutralizing the suspension, and
  - c) isolating cold water-insoluble hydroxyalkylamylose
- (see Claims 1 and 7, page 1, right column, paragraphs 2 and 6).

From page 2, right column, lines 87-89 of the Staley patent, it can be seen that for the etherification, the reaction mixture is heated at a temperature from 30 to 90°C for preferably approximately 1 to 24 hours.

By contrast, in the present application, the etherification (i.e. hydroxyethylation) is carried out at room temperature for 6 to 10 hours, preferably 7 to 8 hours; see page 8, paragraph 3, Claims 4 and 6 of the present application. In Example 2 (see page 5, right

column, paragraph 1), the pH value was between 11 and 12 (according to the present application 10N NaOH is added to prevent the pH value dropping below 12; see Claim 5 and page 8, paragraph 3 of the present application). Other pH-statements cannot be gathered from the Staley patent, in connection with the etherification step.

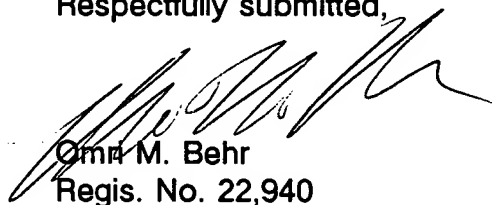
The above statements clearly show that the claimed HES product and the claimed process are different from the product and process disclosed in the Staley patent, and further, the claimed HES product and the process were also not made obvious by the teachings of the Staley patent. Therefore reconsideration and withdrawal of the obviousness rejection based on Staley are requested.

In order to advance prosecution, Applicants have added Claims 8 through 11, which are product-by-process claims which, it is believed, are properly examinable with Group I and are believed patentable for the reasons set forth above.

In view of the above statements, Applicants are of the opinion that the claimed HES are not anticipated by the state of the art as cited by the Examiner, but are novel and inventive.

In view of the above, advancement of the pending claims to issue is requested.

Respectfully submitted,

  
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